demonstrate that in order to get a handle on the origins and maintenance of microbial diversity, the evolution of interactions must be considered and examined in a spatial context.

References

1. Finlay, B.J. (2002). Global dispersal of free-living microbial eukaryote species. Science *296*, 1061–1063.
2. Whitaker, R.J., Grogan, D.W., and Taylor, J.W. (2003). Geographic barriers isolated endemic population of hyperthermophilic archaea. Science *301*, 976–978.
3. Cho, J.-C., and Tiedje, J.M. (2000). Biogeography and degree of endemicity of fluorescent Pseudomonas strains in soil. Appl. Environ. Microbiol. *66*, 5448–5456.
4. Vos, M., and Velicer, G.J. (2008). Isolation by distance in the spore-forming soil bacterium Myxococcus xanthus. Curr. Biol. *18*, 386–391.
5. Whitaker, R. (2006). Allopatric origins of microbial species. Phil. Trans. R. Soc. Lond. B *361*, 1975–1984.
6. Held, N.L., and Whitaker, R.J. (2009). Viral biogeography revealed by signatures in *Sulfolobus islandicus* genomes. Environ. Microbiol. *11*, 457–466.
7. Thompson, J.N., and Cunningham, B.M. (2002). Geographic structure and dynamics of coevolutionary selection. Nature *417*, 735–738.
8. Forde, S.E., Thompson, J.N., and Bohannan, B.J.M. (2004). Adaptation varies through space and time in a coevolving host-parasitoid interaction. Nature *431*, 841–844.
9. Little, A.E.F., Robinson, C.J., Peterson, S.B., Raffa, K.F., and Handelsman, J. (2008). Rules of engagement: interspecies interactions that regulate microbial communities. Annu. Rev. Microbiol. *62*, 375–401.
10. Vos, M., Birkett, P.J., Birch, E., Griffiths, R.I., and Buckling, A. (2009). Local adaptation of bacteriophages to their bacterial hosts in soil. Science *325*, 833.
11. Huber, J.A., Mark Welch, D.B., Morrison, H.G., Huse, S.M., Neal, P.R., Butterfield, D.A., and Sogin, M.L. (2007). Microbial population structures in the deep marine biosphere. Science *318*, 97–100.
12. Kassen, R., and Rainey, P.B. (2004). The ecology and genetics of microbial diversity. Annu. Rev. Microbiol. *58*, 207–231.
13. Vos, M., and Velicer, G.J. (2009). Social conflict in centimeter- and global-scale populations of the bacterium *Myxococcus xanthus*. Curr. Biol. *19*, 1763–1767.
14. Ostrowski, E.A., Katoh, M., Shaulsky, G., Queller, D.C., and Strassmann, J.E. (2008). Kin discrimination increases with genetic distance in a social amoeba. PLoS Biol. *6*, e287.
15. Thompson, J. (2005). The Geographic Mosaic of Coevolution (Chicago: University of Chicago Press).
16. Buckling, A., and Hodgson, D.J. (2007). Short-term rates of parasite evolution predict the evolution of host diversity. J. Evol. Biol. *20*, 1682–1688.
17. Reno, M.L., Held, N.L., Fields, C.J., Burke, P.V., and Whitaker, R.J. (2009). Biogeography of the Sulfolobus islandicus pan-genome. Proc. Natl. Acad. Sci. USA *106*, 8605–8610.
18. Tettelin, H., Masignani, V., Cieslewicz, M.J., Donati, C., Medini, D., *et al*. (2005). Genome analysis of multiple pathogenic isolates of *Streptococcus agalactiae*: Implications for the microbial "pan-genome. Proc. Natl. Acad. Sci. USA *102*, 13950–13955.
19. Fiegna, F., and Velicer, G.J. (2005). Exploitative and hierarchical antagonism in a cooperative bacterium. PLoS Biol. *3*, e370.
20. Hoeksema, J.D., and Forde, S.E. (2008). A meta-analysis of factors affecting local adaptation between interacting species. Am. Nat. *171*, 275–290.

Department of Microbiology, University of Illinois, Urbana-Champaign, 601 S. Goodwin Avenue, Urbana, IL 61801, USA.
E-mail: rwhitaker@life.uiuc.edu

DOI: 10.1016/j.cub.2009.09.035

Neuroscience: The Chain Reaction of Dendritic Integration

Central neurons receive thousands of synaptic inputs. A recent study shows how pyramidal neurons of the mammalian neocortex integrate synaptic input in a parallel manner, illustrating how a chain of dendritic integration mechanisms act to signal distal dendritic excitatory synaptic input.

Stephen R. Williams and Christian Wozny

Nerve cells of the central nervous system are connected into intricate networks by synapses. A long-standing problem in neuroscience is how neurons integrate the many thousands of synaptic inputs they receive to generate output signals, termed action potentials. This problem is by no means trivial, as synapses are positioned throughout the elaborate dendritic trees of central neurons. Because of the biophysical properties of neurons, the electrical impact of synapses diminishes with distance, meaning that synapses positioned remotely in the dendritic tree, far from the site of action potential generation, will only very weakly influence neuronal output [1]. In a recent paper, Larkum *et al.* [2] show that excitatory synaptic input to the most remote parts of the dendritic tree powerfully controls neuronal output through a chain of dendritic integration compartments.

If we were to engineer neurons, it would be logical to place synapses important for the operation of a neuronal circuit close to the site of action potential generation to ensure they have a powerful impact on neuronal output. In the nervous system, however, distinct synaptic pathways are targeted to remote dendritic sites. One beautiful example of this lies in the neocortex. Layer 5 neocortical pyramidal neurons have a complex dendritic tree, with a field of dendrites surrounding the cell body, close to the site of action potential generation, and a second field attached via a long dendritic cable nearly a millimetre away from the cell body, referred to as the apical dendritic tuft (Figure 1). The apical dendritic tuft of layer 5 pyramidal neurons receives two important streams of excitatory input, originating from the thalamus [3] and surrounding neocortical areas [4]. Larkum *et al.* [2] explored the way that excitatory synaptic input is integrated in the apical dendritic tuft of this class of neocortical pyramidal neuron.

Using imaging technology to guide electrical recordings from the fine branches of the apical dendritic tuft of layer 5 neocortical pyramidal neurons, Larkum *et al.* [2] were able to show that non-linear excitatory synaptic integration occurs independently in branches of the apical dendritic tuft (Figure 1, green traces). Surprisingly, this is not the end of the integrative process, as the results of integration in each dendritic branch are fed to a common site of integration, situated in the main apical dendritic trunk of layer 5 pyramidal neurons (Figure 1, red trace). If a critical voltage threshold is reached at this site, a large regenerative dendritic spike is evoked that propagates to the axon to trigger action potential output [5] (Figure 1, blue trace).

There are many factors that contribute to the complex nature of this integration process. First, Larkum *et al.* [2] demonstrated that unitary excitatory postsynaptic potentials (EPSPs) generated in the apical dendritic tuft attenuate massively as they spread to the main apical dendritic trunk, suggesting that apical dendritic

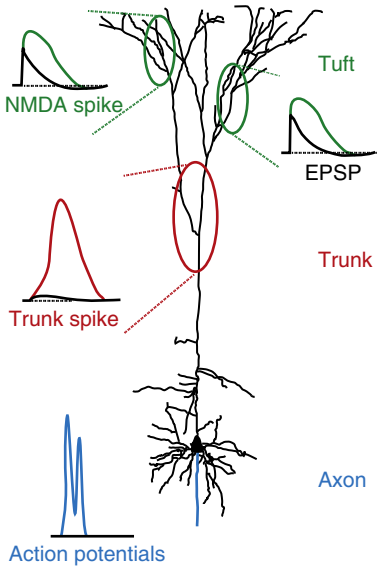

Figure 1. Schematic representation of integration compartments in a neocortical pyramidal neuron.

tuft excitatory synapses have a weak direct signalling role at the dendritic trunk spike initiation zone. To overcome this, excitatory inputs are amplified close to their site of generation.

Larkum *et al.* [2] found that, when groups of excitatory synapses are activated by electrical stimuli, the amplitude and duration of EPSPs are amplified by the generation of spikes dependent on the N-methyl-D-aspartic acid (NMDA) class of glutamate receptors (Figure 1, green traces). At the most excitatory synapses in the mammalian brain, glutamate is the principal excitatory neurotransmitter. Synaptically released glutamate binds to two main classes of postsynaptic receptor, amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and NMDA receptors, which are enriched at the synapse. Unitary EPSPs are mostly mediated by the AMPA receptor conductance; however, if a number of neighbouring excitatory synapses are activated, the voltage-dependent NMDA receptor conductance becomes significant and can lead to the generation of a regenerative spike-like response, termed an NMDA spike [6]. Because of the fine calibre and proximity to a sealed end, EPSPs generated in the terminal dendrites of pyramidal neurons are of large amplitude; consequently the recruitment of only a few (<10) excitatory synapses can lead to the generation of NMDA spikes, which act to dramatically amplify synaptic efficacy [2].

Importantly, Larkum *et al.* [2] were able to show that individual branches of the apical dendritic tuft can perform this operation in relative isolation, with minimal crosstalk between branches of the apical dendritic tuft. The next step in this three-step dance is crucial: the authors found that NMDA spikes in individual branches are not powerful enough to evoke an apical dendritic trunk spike, but the activation of two or more braches is (Figure 1, green traces). Furthermore, computer simulation revealed that the generation of NMDA spikes greatly reduced the number of activated excitatory synapses necessary for the generation of an apical dendritic trunk spike. Thus, the apical dendritic trunk appears to function as an integrator of active processing in individual apical dendritic tuft branches, as suggested by computer modelling [7].

This is certainly an attractive scheme, but many pieces of the puzzle are missing. Focal electrical stimuli are far from physiological, synchronously activating excitatory synapses at discrete dendritic sites. Furthermore, focal electrical stimulation gives no information about the nature of the presynaptic axons activated; do presynaptic neurons that target the apical dendritic tuft make synaptic contacts clustered on individual branches or are they distributed throughout the apical dendritic tuft? Moreover, what is the role of synaptic inhibition, and can NMDA spikes be evoked under higher conductance *in vivo* conditions [8]? The integration scheme highlighted by Larkum *et al.* [2] also appears to diverge from that found in related neuronal classes, such as CA1 pyramidal neurons, where active dendritic spike mechanisms mediated by the recruitment of voltage-activated sodium channels are operational in fine calibre dendritic branches [9].

The new work [2], however, provides important insight into the way neocortical pyramidal neurons operate. A striking parallel between dendritic integration in the apical dendritic tuft and the basal dendritic tree, which surrounds the soma, seems to emerge [2,10]. In both trees, NMDA spikes are operational in single dendritic branches and in both dendritic trees, NMDA spikes are integrated at common collection sites, the apical dendritic trunk and axon initial segment, respectively (Figure 1). Thus, the layer 5 neocortical pyramidal neuron seems to behave as two neurons in one, when synaptic input is focussed either to the basal or apical dendritic tree. This is not the end of the story, however, as co-operative integration can occur when axo-somatic and apical dendritic trunk integration compartments are co-activated [11,12]. In order to gauge the repertoire of synaptic integration in neocortical pyramidal neurons, therefore, new methods must be developed to drive, in a physiological manner, known excitatory and inhibitory pathways that target determined dendritic sites. Only with this information can we ascertain the role of the dendritic integration in neocortical circuit operation.

References

1. Williams, S.R., and Stuart, G.J. (2003). Role of dendritic synapse location in the control of action potential output. Trends Neurosci. *26*, 147–154.
2. Larkum, M.E., Nevian, T., Sandler, M., Polsky, A., and Schiller, J. (2009). Synaptic integration in tuft dendrites of layer 5 pyramidal neurons: a new unifying principle. Science *325*, 756–760.
3. Rubio-Garrido, P., Perez-de-Manzo, F., Porrero, C., Galazo, M.J., and Clasca, F. (2009). Thalamic input to distal apical dendrites in neocortical layer 1 Is massive and highly convergent. Cereb. Cortex *19*, 2380–2395.
4. Petreanu, L., Mao, T., Sternson, S.M., and Svoboda, K. (2009). The subcellular organization of neocortical excitatory connections. Nature *457*, 1142–1145.
5. Williams, S.R., and Stuart, G.J. (2002). Dependence of EPSP efficacy on synapse location in neocortical pyramidal neurons. Science *295*, 1907–1910.
6. Schiller, J., Major, G., Koester, H.J., and Schiller, Y. (2000). NMDA spikes in basal dendrites of cortical pyramidal neurons. Nature *404*, 285–289.
7. Rhodes, P.A., and Llinas, R.R. (2001). Apical tuft input efficacy in layer 5 pyramidal cells from rat visual cortex. J. Physiol. *536*, 167–187.
8. Destexhe, A., Rudolph, M., and Pare, D. (2003). The high-conductance state of neocortical neurons in vivo. Nat. Rev. Neurosci. *4*, 739–751.
9. Losonczy, A., Makara, J.K., and Magee, J.C. (2008). Compartmentalized dendritic plasticity and input feature storage in neurons. Nature *452*, 436–441.
10. Nevian, T., Larkum, M.E., Polsky, A., and Schiller, J. (2007). Properties of basal dendrites of layer 5 pyramidal neurons: a direct patch-clamp recording study. Nat. Neurosci. *10*, 206–214.
11. Larkum, M.E., Senn, W., and Luscher, H.R. (2004). Top-down dendritic input increases the gain of layer 5 pyramidal neurons. Cereb. Cortex *14*, 1059–1070.
12. Williams, S.R. (2005). Encoding and decoding of dendritic excitation during active states in pyramidal neurons. J. Neurosci. *25*, 5894–5902.

MRC Laboratory of Molecular Biology, Hills Road, Cambridge, CB2 0QH, UK.
E-mail: srw@mrc-lmb.cam.ac.uk

DOI: 10.1016/j.cub.2009.08.031